Journal of Cardiovascular Pharmacology
6:S457–S464 © 1984 Raven Press, New York

Sodium Balance and Peripheral Resistance in Arterial Hypertension

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Summary: In this brief review, some aspects of the relation between sodium balance and peripheral resistance in four types of arterial hypertension are discussed. Renal hypertension, hypertension caused by reduced kidney mass and sodium load, mineralocorticoid hypertension, and spontaneous or "genetic" hypertension in rats are considered. In all these forms of hypertension, the increase in peripheral resistance is preceded by changes in body sodium and fluids. However, the precise role of these changes in the development of the subsequent rise of peripheral resistance is not yet clear. Changes in ion transport across the cell membranes have been demonstrated even before the development of hypertension, especially the forms caused by mineralocorticoids or genetic factors. Even though we do not know the underlying mechanisms, it is very likely that these cell-membrane changes are involved in the rise of peripheral resistance and blood pressure. **Key Words:** Na balance—Body fluids—Peripheral resistance—Hypertension.

Renal sodium retention caused by different types of kidney abnormalities or by increased sodium intake, particularly when accompanied by administration of mineralocorticoid hormones or reduced kidney mass, may lead to hypertension through an increase in peripheral resistance. Many hypotheses have been proposed to explain the mechanisms causing the increase in peripheral resistance after changes in sodium balance, but none has been able to reconcile all the experimental data so far accumulated. In this brief review, we shall not present a unifying view but only consider those experimental findings that in our opinion allow us to focus some of the most important aspects of this issue.

Two approaches have been used to study the relation between sodium balance and hypertension: (a) the measurement of changes in body fluids and hemodynamics and (b) the measurement in different types of cells of intracellular sodium, cell-membrane ion transport, or humoral factors affecting these two parameters, on the assumption that they may reflect parallel changes occurring in the vascular smooth-muscle cells more directly involved in the regulation of peripheral resistance *in vivo*.

We shall consider these two approaches briefly in the following four forms of hypertension: (a) renal artery constriction in dogs and rats; (b) sodium load in dogs with reduced kidney mass; (c) sodium load plus mineralocorticoids in rats with reduced kidney mass; (d) spontaneous hypertension in rats.

RENAL ARTERY CONSTRICTION IN THE DOG

One of the first experimental approaches in the study of the role of sodium balance in the regulation of peripheral resistance was the measurement of the changes in sodium balance, body fluids, and hemodynamics after renal artery constriction in dogs and rats, in order to determine whether or not a transient phase of sodium retention with a consequent expansion of body fluids and an increase in cardiac output had a causal or permissive role in the subsequent development of a stable increase in peripheral resistance.

Figure 1 shows our experimental approach to this issue (1). The experiments were conducted in previously uninephrectomized conscious animals with an open-clip device implanted on the renal artery

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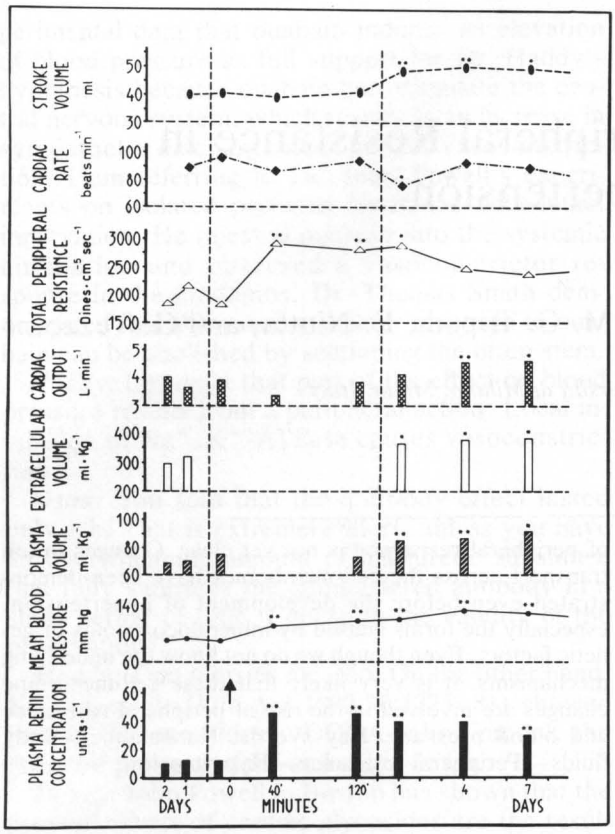

FIG. 1. Average changes in stroke volume, cardiac rate, total peripheral resistance, cardiac output, extracellular volume, plasma volume, mean blood pressure, and plasma renin concentration produced by the renal artery constriction in dogs. Statistical comparison with the mean of basal values: *, $0.005 < p < 0.05$; **$p < 0.005$.

of the remaining kidney. The clip could be closed many days after surgery in the conscious, completely recovered animal. It was then possible to record stroke volume, heart rate, total peripheral resistance, cardiac output, extracellular fluid volume, plasma volume, mean blood pressure, plasma renin concentration and, not shown in the figure, the external sodium balance, since the animal was in a metabolic cage. The recordings started two days before the clip was constricted and were carried on, wherever possible, for at least 12 days. The sequence of events after constriction of the clip can be summarized as follows: a first phase, lasting some hours, during which there was a rise in blood pressure, total peripheral resistance, and renin, the increase in plasma renin being sufficient to explain the rise in peripheral resistance; a second phase, lasting a few days, in which an increase in cardiac output, plasma and extracellular fluid volumes, and renal sodium excretion was observed; and a third phase, not shown in the figure, when cardiac output, plasma and extracellular fluid volumes, and renin and sodium balance tended to return toward normal values, whereas only the peripheral resistance remained high enough to sustain the elevated blood pressure. The sequence of events observed experimentally bears a striking resemblance to the one found by Guyton et al. in the computer model of the overall circulation, when they simulated a stenosis of the renal artery and postulated an oversecretion of renin and renal retention of sodium as the mechanisms responsible for hypertension (Fig. 2) (2).

When all or some of these factors were measured by others before and after renal artery constriction in conscious dogs, the results obtained were all consistent with the sequence of events shown in Fig. 1 (3,4). However, this sequence was not observed when different manipulations of sodium balance in dogs, rabbits, or rats were applied during and after the development of hypertension caused by various kidney lesions produced in anesthetized animals (5-8). Thus, it was suggested that renal sodium retention accompanied by the transient changes in body fluids and cardiac output has no causal or permissive role in the subsequent rise of peripheral resistances.

To demonstrate the influence of anesthesia and surgery on the changes caused by kidney manipulations, the experiments shown in Fig. 3 will be briefly discussed (9). Blood pressure and plasma renin were measured in instrumented two-kidney

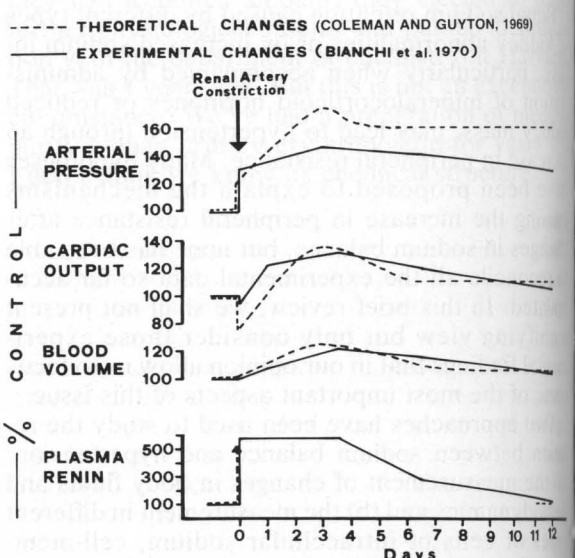

FIG. 2. Comparison between the changes, expressed as percent of control values, in arterial pressure, cardiac output, blood volume, and plasma renin observed in conscious dogs when the renal artery of the lone remaining kidney is constricted (Bianchi et al., ref. 1) (solid lines) and the predicted changes derived from the computer-model analysis (Guyton et al., ref. 12) of this system (dotted lines). Assumptions made in the mathematical model include as hypertensive mechanisms, increased renin secretion and fluid-retention responses to renal artery constriction.

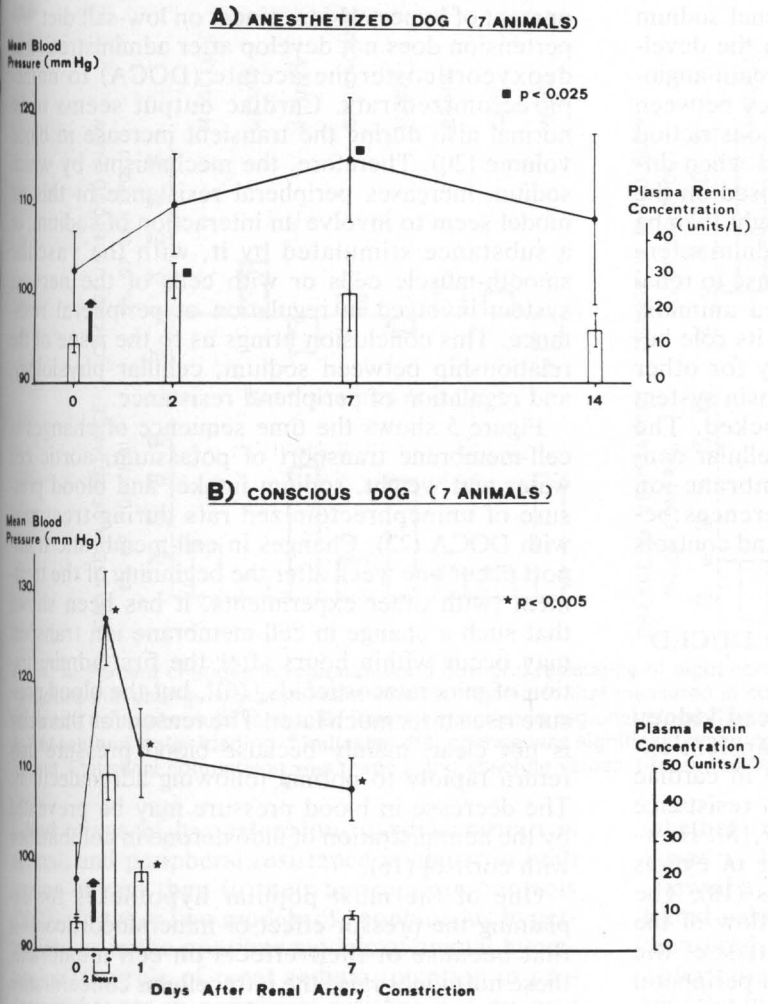

FIG. 3. Effect of renal artery constriction on mean blood pressure and plasma renin concentrations in dogs with intact opposite kidney. The constriction was carried out when the constrictor was placed on the renal artery in A or 15 days later, while the dogs were conscious, in B. (For details see Bianchi et al., ref. 9.)

dogs before and after the same degree of constriction in one renal artery, the constriction being carried out (a) under anesthesia during implantation of the constrictor device and (b) in conscious dogs some days after implantation of the same constrictor device. Blood pressure and plasma renin were also measured in the dogs of group (b) before and after implantation of the constrictor device; thus they served as sham-operated controls for the experiments under (a). These results are not shown in the figure because the blood pressure and plasma renin levels, at the time intervals of the experiments in (a), were not affected by surgery and anesthesia. In condition (b), the initial changes in blood pressure and plasma renin ran parallel, whereas in condition (a), the higher level of renin occurred on day 2 and that of blood pressure on day 7. As no changes were observed in the sham-operated animals, the conclusion drawn from the two experiments may be quite different: the changes in plasma renin may be either relevant (b) or not relevant (a) to the rise in blood pressure after renal artery constriction. Moreover, the time-course changes of blood pressure were quite different in the two experimental situations. Even though blood pressure and renin changes may not be strictly related to sodium balance and peripheral resistance, the experiments shown in Fig. 3 clearly indicate that the common practice of comparing animals exposed to a given experimental manipulation with sham-operated controls, on the assumption that the difference between the two situations may reflect the changes occurring in conscious and undisturbed animals, may provide misleading conclusions.

Certainly, both in dogs and in rats, renal artery constriction may raise blood pressure even in animals on low-salt diet (10–13). However, when both low-salt diet and inhibition of the renin-angiotensin system are applied simultaneously, the development of hypertension is delayed until two to three days after stopping infusion of the blocker of the renin-angiotensin system (14). From these experi-

ments, it is possible to conclude that renal sodium retention may have a permissive role in the development of hypertension only when the renin-angiotensin system is blocked. The discrepancy between the findings obtained after renal artery constriction in conscious animals and those obtained when different types of changes were superimposed on the maneuver of renal artery constriction might then be explained in the following way: renal sodium retention is a normal component of the response to renal ischemia in conscious and undisturbed animals, without any permissive role. However, its role becomes permissive when the possibility for other pressor systems (e.g., the renin-angiotensin system or others) of coming into play is blocked. The studies so far carried out on the intracellular concentration of sodium and on cell-membrane ion transport did not show clear-cut differences between animals with renal hypertension and controls (15,16).

SODIUM LOAD IN DOGS WITH REDUCED KIDNEY MASS

The sodium load in dogs with reduced kidney mass produces hypertension with a transient expansion of body fluids and an increase in cardiac output, followed by a rise in peripheral resistance with normalization of cardiac output (17,18). However, as shown in Fig. 4, this sequence of events does not occur in all the vascular beds (18). The greater portion of the increased blood flow of the initial phase goes through muscular tissue, the brain, and the heart, whereas the rise in peripheral resistance in the later phase occurs mainly in the kidney, the splanchnic bed, the brain, and the bone. The author (18) concluded that "the inhomogeneous nature of the resistance changes makes it unlikely that high blood pressure develops as a result of the operation of a single generalized vasoconstrictor mechanism either nervous or humoral." However, the possibility of a difference in the response of the various vascular beds to the same generalized vasoconstrictor mechanism must be taken into account (19).

SODIUM LOAD + MINERALOCORTICOIDS IN RATS WITH REDUCED KIDNEY MASS

High sodium intake, accompanied by administration of mineralocorticoid hormones, in rats with reduced kidney mass produces a gradual increase in blood pressure over a period of weeks and a transient expansion of body fluids (20,21). The expansion of body fluids does not seem to be necessary for the development of hypertension, since it occurs also in animals on a normal salt diet where no change in body fluids is observed (21). However, some amount of sodium is necessary for the development of hypertension, since, on low-salt diet, hypertension does not develop after administration of deoxycorticosterone acetate (DOCA) to uninephrectomized rats. Cardiac output seems to be normal also during the transient increase in blood volume (20). Therefore, the mechanisms by which sodium increases peripheral resistance in this rat model seem to involve an interaction of sodium, or a substance stimulated by it, with the vascular smooth-muscle cells or with cells of the nervous system involved in regulation of peripheral resistance. This conclusion brings us to the issue of the relationship between sodium, cellular physiology and regulation of peripheral resistance.

Figure 5 shows the time sequence of changes in cell-membrane transport of potassium, aortic cell water and weight, sodium intake, and blood pressure of uninephrectomized rats during treatment with DOCA (22). Changes in cell-membrane transport occur one week after the beginning of the treatment [with other experiments, it has been shown that such a change in cell-membrane ion transport may occur within hours after the first administration of mineralocorticoids (16)], but the blood pressure rise starts much later. The reason for this delay is not clear, mainly because blood pressure may return rapidly to normal following adrenalectomy. The decrease in blood pressure may be prevented by the administration of aldosterone in combination with cortisol (16).

One of the most popular hypotheses for explaining the pressor effect of mineralocorticoids is that because of their effects on cell membrane, these hormones raise the intracellular concentration of sodium within the vascular smooth-muscle cells, thus increasing their contractility. However, in freshly excised vascular tissue incubated with aldosterone, intracellular concentration of sodium decreases (22), and moreover, no clear-cut increase in intracellular concentration of sodium has been found in this form of hypertension (15,16). The most constant finding is an increased cell-membrane permeability to ions (23), but the mechanisms by which this membrane abnormality triggers the sequence of events leading to the rise in peripheral resistance are open to discussion. One possibility is the stimulation of a humoral factor, as discussed by Haddy in this volume.

SPONTANEOUS HYPERTENSION IN RATS

The development of spontaneous hypertension in rats is accompanied by renal retention of sodium both in the spontaneously hypertensive rat (SHR) and in the MHS (24,25). A transient increase of cardiac output in the early phase has been shown in SHR (26), whereas in MHS a continuous measurement of cardiac output during the developmental phase has not been carried out yet. At the estab-

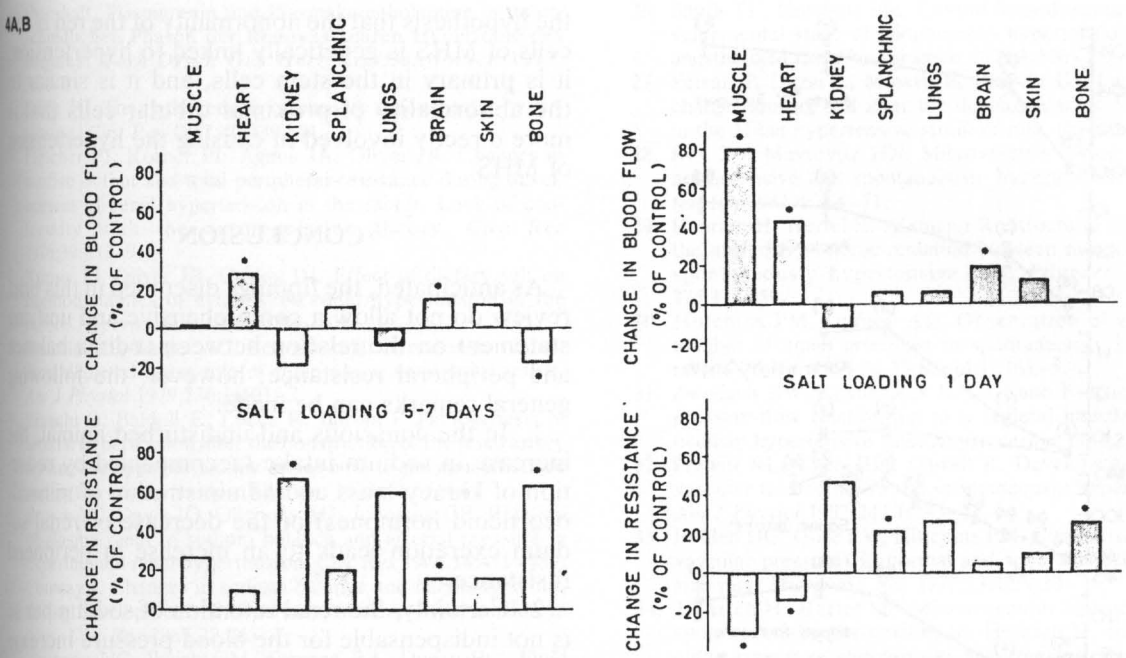

FIG. 4. **A:** Percent changes in regional blood flow and resistance of eight conscious dogs on day 1 of salt and water loading. * Indicates that change was significant when compared to that measured in control group (not shown). Statistical comparison was made using absolute values. **B:** Percent changes in regional blood flow and resistance of eight conscious dogs on days 5–7 of salt and water loading. * Indicates that change was significant when compared to that measured in control group (not shown). Statistical comparison was made using absolute values. (Reprinted from Liard, ref. 18, by permission.)

lished phase of hypertension, cardiac output is normal, and peripheral resistance is higher in both strains of rats than in their appropriate controls (26,27). In these two models of spontaneous hypertension, as in the previous models of animal hypertension, the role of renal sodium retention in producing changes in peripheral resistance is open to discussion.

Many studies are available on microcirculation in SHR; therefore, it should be possible to understand better the mechanism of the increase in peripheral resistance. When comparing SHR with their controls Wistar-Kyoto rats (WKY) regarding the pattern of the vascular bed going from the feeding arterioles (A_1), ranging in size from 60 to 120 μm, down to capillaries and up again to the small vein (V_1) of 100–204 μm, the following emerges: With one exception (28), various authors have found that the inner diameter of the small arterioles tends to be larger in SHR (29–31). Calculation of the apparent segmental resistance showed, in SHR, lower values of A_1 and higher values of the smallest arterioles. The number of arterioles per unit of tissue is decreased in SHR (29,30,32), and this may be one of the most important causes of the increase in cross-sectional resistance. The higher values of inner diameter in the feeding arterioles A_1 of SHR with the calculated lower resistance of this segment of circulation clearly indicate the nonhomogeneity of the mechanisms regulating vascular tone even in the same vascular bed. The most important issue is whether or not the hydrostatic pressure of capillaries is higher in SHR; some authors (33,34) showed a higher value in SHR, whereas others (31) found values similar to those in WKY. The former measured pressure in cremasteric muscle or mesenteric tissue, and the latter used spinotrapezius muscle; but apart from this difference, there are no apparent explanations for this discrepancy. In fact, if the hydrostatic pressure within the capillaries were higher in all the vascular beds of SHR, it would be rather difficult to reconcile this finding with a pressor mechanism involving primarily the small resistance vessels.

Numerous studies (35–37) have been carried out on red blood cells of both SHR and MHS, assuming that a genetically determined abnormality in cell handling of sodium could be found also in this type of cell. In this way, red blood cells could be used to study those genetic cellular mechanisms that, at the level of the vascular smooth-muscle cells or other nervous or renal cells, could be directly involved in the regulation of blood pressure. Without taking any position on the question of whether or not red blood cell changes may mirror vascular smooth-muscle cell changes, some interesting differences have been found when red blood cells of MHS or SHR were compared with those of their appropriate controls. In MHS, intracellular concentration of sodium tends to be lower and sodium-potassium outward cotransport tends to be higher (38); whereas in SHR, the changes in these two fac-

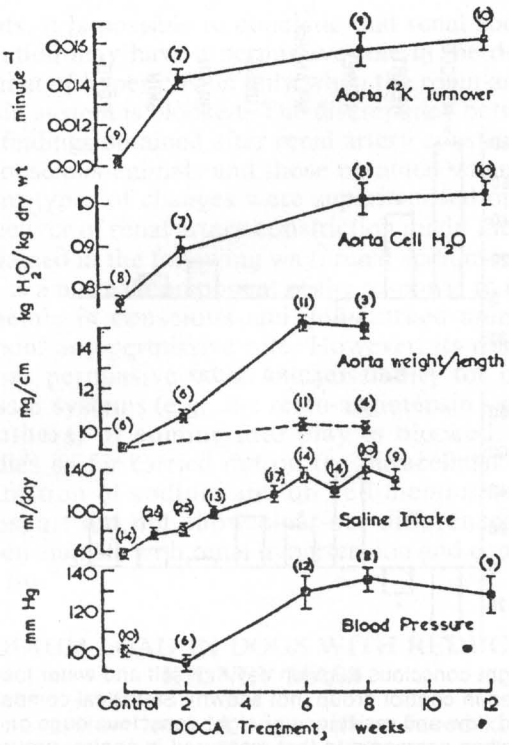

FIG. 5. Effects of the duration of the treatment with DOCA plus saline on the rat aorta, saline intake, and blood pressure. Circles indicate control rats; squares indicate treated rats. The number of rats observed appears in parentheses. Averages ± SE are connected by straight lines. (Reprinted from Jones and Hart, ref. 22.)

tors are just the opposite: lower sodium-potassium cotransport and tendency to a higher intracellular concentration of sodium (39). Other studies, reported in detail elsewhere (40,41), indicate that the kidney has a key role in the development of hypertension in MHS, very likely owing to a primary increase in tubular reabsorption. On the contrary, vascular smooth-muscle reactivity and central nervous system changes seem to be more important in the pathogenesis of hypertension of SHR (42). As a decrease in intracellular concentration of sodium within the tubular cells may favor tubular reabsorption (43), and an increase in intracellular sodium in vascular smooth-muscle or nervous cells may stimulate contractility or reactivity (44), one may speculate that the two patterns of red blood cell changes in MHS and SHR are related to the different genetic mechanisms responsible for hypertension in the two strains of rats.

The relation between red blood cell and proximal tubular cell in MHS has been discussed in detail elsewhere (45). The results obtained with bone marrow transplantation, genetic analysis on (MHS × MNS) F_2 hybrids, and measurements of cell volume, of sodium transport across the cell membrane, and of intracellular concentration of sodium on the two types of cells were consistent with the hypothesis that the abnormality of the red blood cells of MHS is genetically linked to hypertension; it is primary in the stem cells, and it is similar to the abnormality of proximal tubular cells that is more directly involved in causing the hypertension of MHS.

CONCLUSION

As anticipated, the findings discussed in this brief review do not allow a comprehensive and unifying statement on the relation between sodium balance and peripheral resistance; however, the following general remarks can be made:

1. In the conscious and undisturbed animal, the increase in sodium intake (accompanied by reduction of kidney mass and administration of mineralocorticoid hormones) or the decrease of renal sodium excretion leads to an increase in peripheral resistance.
2. Certainly, the renal retention of sodium per se is not indispensable for the blood pressure increase observed after a renal injury. However, when the renin-angiotensin system is blocked, renovascular hypertension does not develop in rats fed with a low-salt diet. Thus, in this circumstance, sodium seems to have a permissive role in the development of hypertension. However, it is not possible to conclude from these data the direct relationship between sodium and peripheral resistance, since the hemodynamics were not measured.
3. Alterations of the cell-membrane ion transport have been demonstrated in hypertension induced either by mineralocorticoid hormones or by genetic mechanisms; however, the sequence of events from these cell-membrane alterations to the rise in peripheral resistance, has not been clarified yet.
4. Two different types of alterations in red blood cell membrane have been found in two genetically hypertensive strains of rats, with two different pathogenetic mechanisms as the cause of their hypertension. In one of these strains (MHS), a clear relationship has been demonstrated between the abnormality in cation transport of red blood cells and that of renal tubular cells.

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Discussion

Hofbauer: Concerning the role of the sympathetic nervous system in transforming volume changes into changes in peripheral resistance, Gavras in Boston has shown that acute saline loading in subtotally nephrectomized rats induces acute hypertension. This is at least partially dependent on an increased sympathetic activity. Similarly, data from Dietz in Heidelberg suggest that the sympathetic nervous system is activated by a high-salt diet.

Bianchi: If you change intracellular sodium concentration in sympathetic nerves, the release of norepinephrine is facilitated. But you can prevent or at least reduce DOCA hypertension by destruction of the sympathetic nervous system. We must remember that cell membranes are also in the sympathetic system, so any change in cell-membrane function may affect the sympathetic nervous system. I mentioned this when I discussed the Japanese strain of rats.

Messmer: Information about microvascular changes and microvascular adjustments is mainly derived from the microcirculation of the mesentery. It would be essential to have this information from the skeletal muscle. Are any microvascular data, especially in connection with electrolyte cotransport, available from the Milan strain of hypertensive rats?

Bianchi: No. I said that there is no agreement on vessel rarification. On the other hand, in the cremasteric muscle, a reduction in the number of vessels has been shown; it is not only in mesenteric vessels. I agree that this is a quite complex field, and I am just referring to the data of the literature. Most of the authors agree that the inner diameter of feeding arterioles is wider in hypertensive than in normotensive rats. How can we reconcile this finding with the idea that the vascular tone is increased? I do not know personally.

Regoli: You said that Milan hypertensive rats and spontaneously hypertensive rats have different lesions and show different modifications in the sodium content and sodium-potassium cotransport. Would you expect that the two modifications cause hypertension by, let us say, increasing calcium influx and therefore vascular reactivity?

Bianchi: This should be discussed, because it seems rather strange that two opposite changes might result in the same response: the increase in blood pressure. Of what we know about the physiology of the renal tubular cells, any genetic mechanism affecting the membrane by decreasing the intracellular concentration of sodium or calcium will facilitate sodium flux across the tubular epithelium. The decrease in cell volume or sodium concentration would facilitate reabsorption. On the other hand, all situations that tend to increase sodium concentration within vascular smooth-muscle cells will enhance vascular tone, at least in some vascular beds. Why does the combination of these two opposite changes not blunt either of them? We are now approaching this problem by crossing the Japanese strain with the Milan strain. We do not have, as you might expect, an explosion of hypertension because we are combining two pressor mechanisms.

Regoli: Are you obtaining normotensive rats?

Bianchi: No, they are not really normotensive, because the Japanese rats have a much higher blood pressure than our rats. They have a mean blood pressure of approximately 180 mm Hg, whereas ours have one of 125–130 mm Hg, and we have got hybrids of 145–150 mm Hg. In my opinion at least, this is a kind of compensation, which might limit the progression of the disease. If only one mechanism were working—say, the smooth-muscle mechanism—without any counterregulatory mechanism, we would have a progressive increase in blood pressure without any possibility of escape; whereas this type of compensation at the kidney level will counteract a progressive increase in blood pressure. These are speculations, of course.

Drayer: In which type of hypertension did you study sodium-potassium cotransport; did all these patients have essential hypertension?

Bianchi: They were people with essential hypertension.

Drayer: Is it indeed true that the electrolyte changes in vascular wall happen in the DOCA-hypertensive rats long before there is any evidence of high blood pressure?

Bianchi: Yes, the change in sodium transport across the membrane occurs earlier. However, there is no proof that, *in vivo,* we get an increase or a decrease in the intracellular concentration of sodium. We have only some observations that in fresh, removed tissue potassium permeability and sodium-potassium pump activity are changed, and very likely this also occurs *in vivo*. I think that today no physiologist will accept any experimental data so far published as a clear evidence for an increasing intracellular sodium concentration *in vivo*.

Aiken: Small vessels tend to be more sensitive to prostaglandins than most readily studied large vessels, like aorta, and prostaglandin production *in vitro* tends to be greater than *in vivo*. It may be that the lack of a contractile effect of ouabain is due to the antagonism by endogenous prostaglandin production, which would be of no consequence in the aorta because there are no vasodilator receptors for prostaglandins.

Bianchi: This is probably true: I mentioned that despite the lack of an increasing tone, there was an increase in the intracellular concentration of sodium as well as a change in membrane potential. I do not see why a smooth muscle cannot contract when the membrane potential is changed. It depends on the experimental situation.